U.S. DEPARTMENT OF COMMERCE
National Technical Information Service

PB-253 028-T

STUDIES ON THE ETIOLOGY OF ITAI-ITAI DISEASE

ENVIRONMENTAL PROTECTION AGENCY

1970

BIBLIOGRAPHIC DATA SHEET	1. Report No. EPA TR73-349	2.	PB 253 028

4. Title and Subtitle: Studies on the Etiology of Itai-Itai Disease

5. Report Date: March 10,1970

6.

7. Author(s): Y. Fukuyama and K. Kubota

8. Performing Organization Rept. No.

9. Performing Organization Name and Address: Translated from the Japanese by EPA

10. Project/Task/Work Unit No.

11. Contract/Grant No.

12. Sponsoring Organization Name and Address: EPA ISD Translation Services Division, Library, RTP, NC 27711

13. Type of Report & Period Covered

14.

15. Supplementary Notes: Igaku To Seibutsugaku [Medicine and Biology] 80(3):131-135 March 10. 1970

16. Abstracts

17. Key Words and Document Analysis. 17a. Descriptors

EPAISD
Cadmium
Toxicity

17b. Identifiers/Open-Ended Terms

Cadmium Poisoning
Kidney functions
Cadmium Contamination
Water Pollution

17c. COSATI Field/Group 6-T 57-Y

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U. S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

18. Availability Statement: NTIS is authorized by the copyright holder to reproduce and sell copies of this translation

19. Security Class (This Report) UNCLASSIFIED

20. Security Class (This Page) UNCLASSIFIED

21. No. of Pages 9

22. Price 3.50

148239

ORIG

TR 349-73

6820

STUDIES ON THE ETIOLOGY OF ITAI-ITAI DISEASE

by

Yuzo Fukuyama (Non-Member) and Kentaro Kubota (Member),
Toyama Prefectural Institute of Hygiene and Medical Microbiology.

Published in Igaku To Seibutsugaku, [Medicine and Biology],
Vol. 80, No. 3, March 10, 1970, pp. 131-135.

It is said that itai-itai disease is a Fanconi syndrome [1] caused by chronic cadmium poisoning. No clear conclusion has been reached as yet concerning the reason why many cases of this disease were found among aged muliparae, and almost no cases were found among males.

We have previously reported [2] that an early diagnosis and a differential diagnosis of itai-itai disease were possible by comparing urine gel filtration patterns, and that a presumption of the degree of kidney disorder by the G25 albumin ratio (Folin value ratio of urine albumin to total Folin reaction value) was possible. Afterward, we found that the G25 albumin ratio could also be used as an indication of the degree of kidney disorder caused by chronic cadmium poisoning. Therefore, we have studied the gel filtration patterns of

---

Translated for Information Services Division, EPA, from the Japanese by LEO KANNER ASSOCIATES, P. O. Box 5187, Redwood City, California 94063, (415) 365-3046, January 1973.

urine and the G25 albumin ratio of inhabitants in the area of itai-itai disease incidence and we have studied the life history of patients. As a result of the investigation, cases of kidney disorder caused by chronic cadmium poisoning were found in both sexes, and we came to have the opinion that itai-itai disease was possibly caused by intake of cadmium in great quantities, especially during the period of pregnancy. We will make our report as follows:

Materials and Methods

We collected urine from inhabitants of the area of itai-itai disease incidence, from patients, and from dwellers of another area for comparison, and we kept it at a temperatures of 4°C or -20°C. A gel filtration was performed for each urine sample in accordance with the method mentioned in the previous report [2]. A measurement based on the Folin-Lowry method was taken. We have calculated the G25 albumin ratio from the gel filtration patterns made in the above-mentioned measurement. The history of inhabitants and patients was based on itai-itai disease patient records kept by the Department of Welfare of the Toyama Prefecture.

Results and Considerations

Distribution of the G25 albumin ratio in urine of inhabitants in the area of itai-itai disease incidence, of patients, and of dwellers in the comparative area is shown in Fig. 1. The G25 albumin ratio in the urine of itai-itai disease patients in group I (accompanied by natural fracture) and group i (with osteomalacia) ranged from 24% to 40%; that of urine albumin and glucose in the positive urine group among inhabitants of the itai-itai disease incidence area ranged from 10% to 30%; that of urine albumin and glucose in the negative urine group amoung inhabitants of the itai-itai disease incidence area ranged from 9% to 17%; and that of the inhabitants who moved to the area of disease

incidence after 1945 ranged from 5% to 10%, while that of dwellers of the comparative area showed a value of about 6% or less. A very similar tendency was found among males. The G25 albumin ratio of urine of those who had lived in the cadmium-contaminated area before 1945 ranged from 16% to 27%; that of those who moved to the area after 1945 ranged from 5% to 9%, while that of dwellers of the comparative area also showed a value of 6% or less.

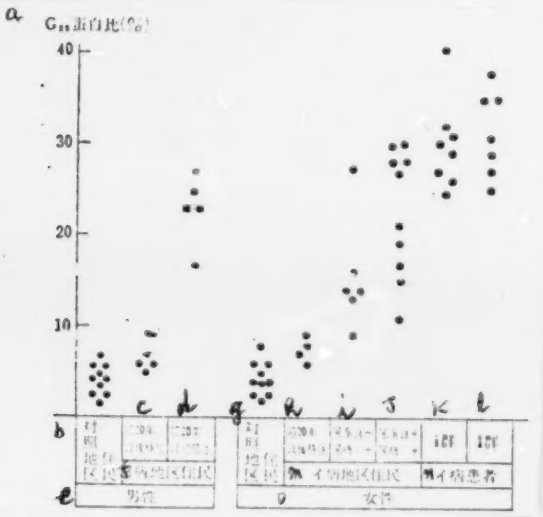

Fig. 1. Kidney disorder caused by chronic cadmium poisoning; G25 albumin ratio.

Key:
a. G25 albumin ration (%)
b. Dweller of the comparative area
c. Those who moved to the area after 1945
d. Those who had lived in the area before 1945
e. Male
f. Inhabitants in the area of itai-itai disease incidence
g. Dwellers in the comparative area
h. Those who moved to the area after 1945
i. Urine albumin -
Glucose in urine -
j. Urine albumin +
Glucose in urine +
k. Group i
l. Group I
m. Inhabitants of the area of itai-itai disease incidence
n. Itai-itai disease patients
o. Female

The G25 albumin ratio in the urine of chronic cadmium-poisoned patients compared to manifestation of clinical symptoms increases in the following orders of groups: those who moved to the cadmium contaminated area after World War II; negative urine albumin group of inhabitants in the cadmium-contaminated area; positive urine albumin group of inhabitants in the same area; group i of itai-itai disease patients; and group I of itai-itai disease patients. From this, we think that the G25 albumin ratio of urine can be used as an indication of the degree of kidney disorder caused by chronic cadmium poisoning.

In order to understand the incidence of ita-itai disease by the indication of the G25 albumin ratio, we studied urine gel patterns, the G25 albumin ratio, and the life history of each case, randomly sampling ten each of male and female inhabitants from Hirota, Yomenaka Machi, the Toyama prefecture, which is one of the areas of itai-itai disease incidence. The outline of the study is shown in Fig. 2. In the life history, we indicated the frequency of pregnancy, period of pregnancy, period of manifestation of subjective symptoms, and period of residence in the cadmium-contaminated area.

According to this figure, the G25 albumin ratio of those who moved to the area after 1949 is 10% or less, and the Sefferdix 9200 [word unknown] gel filtration pattern is also normal. On the other hand, a pattern clearly showing kidney disorder caused by chronic cadmium poisoning and a rise in the G25 albumin ratio is found among inhabitants who lived in the area before 1949. Among cases who lived in the area before 1939, some show a clear pattern of kidney disorder caused by chronic cadmium poisoning in their gel filtration. Among those who lived in the area from 1929 to 1939 at puberty and prime of life, the G25 albumin ratio of some cases shows 20% or more. This suggests that the drinking water was heavily contaminated by cadmium during this period.

Case S.S. was in military service during this period and is thought to have escaped the public hazard of cadmium.

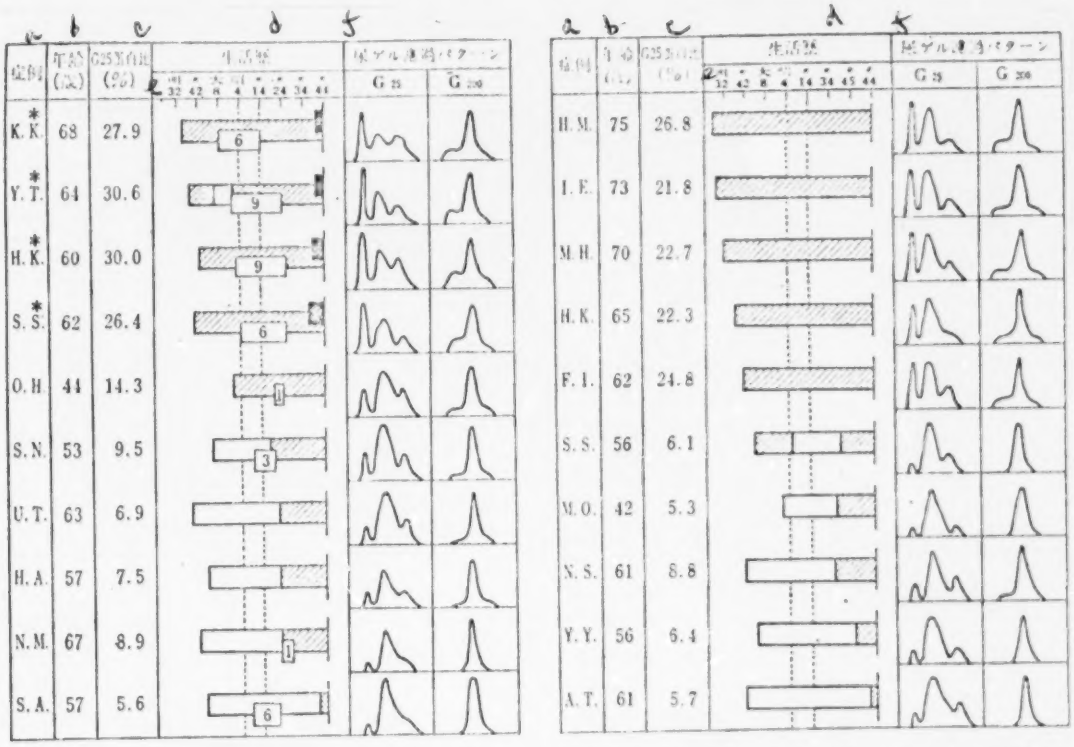

Fig. 2. Life history, urine gel filtration pattern and G25 albumin ratio of inhabitants of Hirota area and of itai-itai disease patients.

Left column is for female, and right for male. In the life history column, the rectangle shows life period. The rectangle with oblique lines shows the residence period in the cadmium-contaminated area. The black portion shows the period when the subjective symptoms were manifested. The rectangle enclosing a number shows the period of pregnancy. The number shows the frequency of pregnancy. * marked is itai-itai disease patients.

Key:
a. Case
b. Age
c. G25 albumin ratio (%)
d. Life history
e. 1899
1909
1919
1929
1939
1949
1959
1969
f. Urine gel filtration pattern

In this figure, the four cases admitted as itai-itai disease patients were all pregnant several times during the period of 1929 to 1939, and the G25 urine albumin ratio is much higher in comparison with that of males. This, we think, is due to a synergistic effect: the burden on the kidneys at the time of pregnancy and cadmium toxicity. Therefore, the kidneys suffered extremely. In order to make the relation between pregnancy and itai-itai disease clearer, we studied the life history of ten itai-itai disease patients each from Hirota, Hagino Shima, and Kutsuwada villages, which are in the area of itai-itai disease incidence (Fig. 3). Arranging each case in order of parity, we noticed that the subjective symptoms of itai-itai disease were manifested at a comparatively late period among the elederly and the younger women of each district, while they were manifested at a comparatively early period among the middle-aged patients.

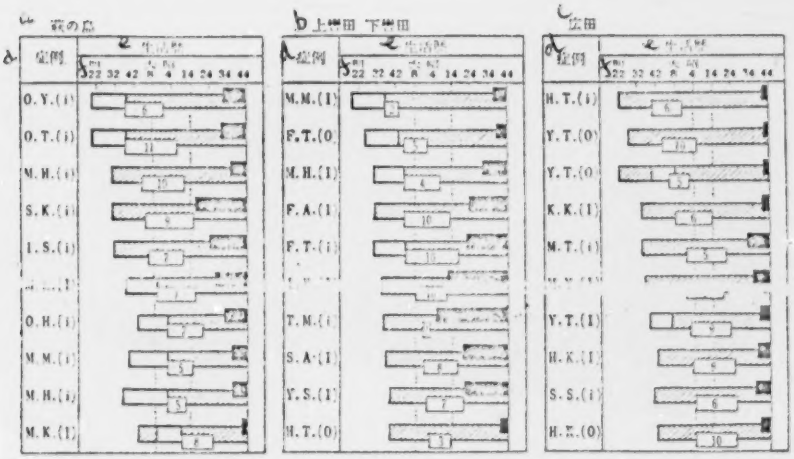

Fig. 3. Life history of itai-itai disease patients in Hagino Shima, Kutsuwada, and the Hirota area. (O) Those requiring observation on itai-itai disease.

Key:
a. Hagino Shima
b. Kami Kutsuwada and Shimo Kutsuwada
c. Hirota
d. Case
e. Life history
f. 1889 1899 1909 1919 1929 1939 1949 1959 1969

This, we think, was due to the intake during pregnancy of a great quantity of drinking water contaminated by a high density of cadmium by patients (whose subjective symptoms were revealed at the earlies period in each area). We think that there was contamination by a high density of cadmium in the districts of Hagino Shima and Kutsuwada from 1919 to 1939. In the Hirota district, this was from 1929 to 1939, as mentioned before. To sum up, we assume that cadmium contamination of the basin of the Jintsu River began about 1902, and from 1919 to 1939 there was a high density of cadmium contamination, from which time the contamination lasted until about 1949.

In studying the growth of annual rings of the Japanese cedar and its cadmium content in the cadmium-contaminated area, Ishizaki [3] reported in 1969 that the maximum cadmium contamination of the basin of the Jintsu River was from 1923 to 1944. This view is practically in accord with our result.

The severe itai-itai disease patients accompanied with natural fracture in each district .....[original text missing from this point on.]